Translated from ***Rev Prescrire*** **April 2012; 32 (342): 268**

Nicorandil: mucocutaneous ulceration (continued)

● **A very severe case report.**

In 2012, a summary of an exemplary case report of adverse effects attributed to *nicorandil* was published in the newsletter of the Regional Pharmacovigilance Centre in Angers, France (1). *Nicorandil* has minor efficacy as a symptomatic treatment for angina pectoris. It is known to cause sometimes severe ulceration of the skin and mucosae (2).

An 87-year-old woman who had been taking *nicorandil* since 2003 developed severe aphthous stomatitis in mid-2009 (1). *Nicorandil* was discontinued in July 2009 and the lesions healed within a month. In August, *nicorandil* was reintroduced.

In December 2009, a sigmoidouterine fistula was diagnosed. In March 2011, a colostomy was performed. Then, a vesicovaginal fistula was diagnosed. The stoma area became ulcerated in August 2011.

Nicorandil was withdrawn in August 2011. By late September 2011, the ulceration around the stoma had improved and the pain had stopped. By November 2011, it has almost completely healed.

In view of *nicorandil*'s minor efficacy in angina, these adverse effects are unacceptable: patients would be better served if *nicorandil* were neither prescribed, used nor licensed.

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Selected references from Prescrire's literature search.
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2- Prescrire Editorial Staff "Painful chronic ulceration linked with nicorandil: the vagina too" *Prescrire Int* 2010; **19** (110): 257.

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Varenicline and bupropion: suicide

● **An analysis of reports in the USA.**

In late 2011 a study based on reports made between 1998 and 2010 to the US Food and Drug Administration (FDA) analysed reactions in patients taking drugs used for smoking cessation, namely *varenicline*, *bupropion* and *nicotine* (1). It included 3249 cases of suicide, self-harm and severe depression, 90% involving varenicline, 7% bupropion, and 3% nicotine.

The authors calculated what proportion these adverse effects represented among all other serious adverse effects reported with each drug.

Compared to *nicotine*, this proportion was 8 times higher with *varenicline* (odds ratio 8.4, 95% confidence interval (95%CI): 6.8 to 10.4) and about 3 times higher with *bupropion* (95%CI: 2.3 to 3.7). The increase persisted after excluding reports in which the patient was also taking one or more of the other 58 drugs for which, according to the US summaries of product characteristics, suicide is an adverse effect.

In practice, *varenicline* and *bupropion* both have an unfavourable harm-benefit balance. When a smoker needs a drug to help him or her quit, it is best to use nicotine (2).

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Selected references from Prescrire's literature search.
1- Moore TJ et al. "Suicidal behaviour and depression in smoking cessation treatments" *Plos One* 2011; **6** (11): 7 pages.
2- Prescrire Rédaction "19-5. Patients en cours de sevrage tabagique" *Rev Prescrire* 2011; **31** (338 suppl. interactions médicamenteuses).

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Venlafaxine: preeclampsia and eclampsia

● **Gestational hypertension.**

In early 2012 the World Health Organization's pharmacovigilance centre in Uppsala published an analysis of 31 cases of hypertensive disorders attributed to *venlafaxine* in pregnant women (1). They derived from the international Vigibase database. There were 4 cases of eclampsia, 21 of preeclampsia, 6 of gestational hypertension and 2 of the Hellp syndrome (severe preeclampsia, haemolysis, thrombocytopenia and liver damage). Only 3 of the women were under 29 years old. The daily doses of *venlafaxine* ranged from 9 to 300 mg and the treatment period ranged from 19 days to several years.

A cohort study of 5731 women showed that the risk of gestational hypertension was roughly twice as high among women taking a selective serotonin reuptake inhibitor antidepressant as in women not taking such drugs (odds ratio 1.9, 95% confidence interval (95%CI) 1.4 to 2.7) (1). The frequency of preeclampsia was 9% in women taking an SSRI and 2.4% in controls, and the risk was even higher with *venlafaxine* (relative risk 4.9, 95% CI: 2.7 to 8.8).

Blood pressure elevation is a well-known adverse effect of *venlafaxine* (2) and is one more reason to use antidepressants sparingly during pregnancy.

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Selected references from Prescrire's literature search.
1- "Venlafaxine, pre-eclampsia, eclampsia and related disorders of pregnancy" *WHO Pharmaceuticals Newsletter* 2012; (1): 19-21.
2- Prescrire Editorial Staff "Venlafaxine and generalised anxiety disorder: minimise recourse to drugs" *Prescrire Int* 2001; **10** (55): 131-134.

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Benfluorex: lesions on a bioprosthetic heart valve too

● **A troubling case.**

In early 2012, a French team published a troubling case report involving a 40-year-old woman who underwent heart valve replacement surgery twice while taking *benfluorex* (formerly marketed under the brand name Mediator° among other names) (1,2).

After 15 months of *benfluorex* therapy, the patient was diagnosed with mitral valve regurgitation, and a bioprosthetic valve was implanted.

Benfluorex was reintroduced, and the patient continued treatment for 33 months. Cardiac problems developed a second time. She was diagnosed with mitral and aortic regurgitation, and both valves were replaced with mechanical valves. The lesions on the bioprosthetic mitral valve resembled those on the native aortic valve, including thickening similar to lesions attributed to *benfluorex* or observed in patients with carcinoid tumours. No other possible causes of valvular heart disease were identified, such as the use of other amphetamine appetite suppressants or ergot derivatives.

Benfluorex therefore also appears to provoke serious valvular injury, even to porcine bioprosthetic valves.

In cases of valvular insufficiency, even those involving a bioprosthetic valve, *benfluorex* should be systematically suspected as the causative agent, along with other drugs known to damage heart valves.

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